PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IB/G-33570/BCK GWK	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/014646	International filing date *(day/month/year)* 22.12.2004	Priority date *(day/month/year)* 23.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07D501/04 C07D501/46		
Applicant SANDOZ AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.10.2005	13.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Rufet, J Telephone No. +49 30 25901-332

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/014646

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-11 as originally filed

   Claims, Numbers

   1-10 received on 19.10.2005 with letter of 07.10.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

Reference is made to the following documents:

D1: J.O.C, vol. 53, no. 5, 1988, pages 983-991, XP002328374
D2: J. OF ANTIBIOTICS, vol. 47, no. 5, 1994, p. 609-612, XP008047135
D3: US-A-4 474 779 (NAGANO ET AL) 2 October 1984
D4: GB-A-2 116180 (BRISTOL-MYERS CO.) 21 September 1983
D5: DE-A-3212900 introduced by Applicant with letter dated 07.10.2005

1. Amendments

New claim 1 is based on claims 1 and 2 as originally filed and therefore acceptable.

2. Novelty

The claimed subject-matter discloses a process for the preparation of an intermediate of formula (I) (claim 1) useful for the preparation of cefepime of formula (V) according to independent claim 11.
The preparation of the intermediate of formula (I) of present claim 1 is carried out by the following steps:

a) desilylation of a N,O-bis-silylated 3-iodomethyl-3-cephem compound of formula (II) into the 7-aminocephalosporanic acid (7-ACA) of formula (III)

b) nucleophilic substitution on the iodomethyl group of compound (III) in order to obtain the desired intermediate (I)

c) finally, intermediate (I) is acylated in order to obtain cefepime (claim 11).

Document D1 discloses a process for the preparation of cefepime using also the N,O-bis-silylated 3-iodomethyl-3-cephem compound of formula (II).
The process of D1 differs in that the desilylation reaction is carried out after the nucleophilic substitution (see D1, p. 984-85).

Document D2 discloses an analogous process for the preparation of quaternary ammonium cephalosporin compounds starting from the 7-ACA compound using steps b) and C) as abovementioned. A desilylation step a) is in D2 not disclosed (see especially scheme 1).

Document D3 does not refer to quaternary ammonium cephalosporin compounds nor to the use of N,O-bis silylated compounds as starting materials. However, the use of 7-ACA compound as starting material (see D3, reference examples 1-4) is described.

Document D4 describes also a process for the preparation of cefepime wherein a compound of formula (I) of present claim 1 may be acylated (see D4, especially claim 18, wherein B1 is hydrogen). However a process for the preparation of compound of formula (I) according to the present claim 1 is in D4 not disclosed nor suggested (see especially p. 19, first paragraph).

Document D5 does not refer to a process for the preparation of cefepime, however this document refers to a process for the preparation of the intermediate compound of formula (III).

The subject-matter of claims 1-10 is therefore considered to be novel (Art.33(2)PCT).

3. Inventive step

An inventive step acknowledgment for new claim 1 should be accepted for the following reasons:

Documents D1-D2 are relevant prior art for the assessment of an inventive step, whereby D1 is considered to represent the closest prior art, since it also refers to a process for the preparation of cefepime using also the N,O-bis-silylated 3-iodomethyl-3-cephem compound of formula (II).

Starting from the closest prior D1, the problem to be solved by the present application may be regarded as the provision of an improved process for the preparation of the Delta-3 cefepime isomer, which is the most antibiotically active isomer (see page 7, lines 11-22 of

the description).

From the technical teaching of D1 and D2 it was not predictable that the claimed process based on the in-situ generation of the intermediate compound (II) would result in the preparation of cefepime in higher yields and purity when compare to the closest process of D1 (claimed process: purity = less than 1% impurities; yields = 65 to 85 % / D1: purity = 7% contamination, yields 35-47%).
In other words, it was not obvious to the skilled person that an in-situ generation of the iodomethyl cephem compound of D2 in the context of the one-pot reaction of D1 would greatly increase both yield and purity of the process of D1.

Dependent claims 2-10 meet therefore the requirements of Art. 33(3) PCT.

Re Item VIII.

There is a typing mistake in page 3, l. 15 of the description, since the compound of formula III is not a N,O-bis-silylated 3-iodomethyl-3-cephem compound (should be formula II, see claim 1).

In page 3, line 16, the number of the cited patent EP612752 seems to be wrong, since this document does not refer to a process for the preparation of the N,O-bis-silylated 3-iodomethyl-3-cephem compound.